PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 06 September 1999 (06.09.99)	
International application No. PCT/EP98/08557	**Applicant's or agent's file reference** BET 98/1029
International filing date (day/month/year) 14 December 1998 (14.12.98)	**Priority date** (day/month/year) 15 December 1997 (15.12.97)
Applicant CHELLY, Jamel et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

07 July 1999 (07.07.99)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO ***34, chemin des Colombettes*** **1211 Geneva 20, Switzerland**	Authorized officer Jean-Marie McAdams
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF DEFECTS IN
THE INTERNATIONAL APPLICATION

(PCT Articles 3(4)(i) and 14(1) and Rule 28.1)

To:
European Patent Office
Postbus 5818
Patentlaan 2
NL-2280 HV Rijswijk
PAYS-BAS

in its capacity as receiving Office

Date of mailing (*day/month/year*) 12 March 1999 (12.03.1999)	
International application No. PCT/EP98/08557	International filing date (*day/month/year*) 14 December 1998 (14.12.1998)
Applicant INSTITUT NATIONAL DE LA SANTE ET DE LA RECHERCHE MEDICALE (INSERM)	

1. ☐ The International Bureau hereby calls the attention of the receiving Office to the defects **in the international application as filed**, which are specified on the attached
   - ☒ Annex A
   - ☐ Annex B1 *(text matter of the international application as filed)*
   - ☐ Annex C1 *(drawings of the international application as filed)*

2. ☐ The International Bureau hereby calls the attention of the receiving Office to the defects **in the translation of the international application** furnished under Rule 12.3, which are specified on the attached
   - ☐ Annex A
   - ☐ Annex B2 *(text matter of the translation of the international application)*
   - ☐ Annex C2 *(drawings of the translation of the international application)*

Additional observations *(if necessary)*:

The International Bureau of WIPO
34, chemin des Colombettes
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Authorized officer
Athina Nickitas-Etienne

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ANNEX A TO FORM PCT/IB/313

national application No.
PCT/EP98/08557

The International Bureau has found the following defects in the international application as filed:

1. As to **signature*** of the international application (Rules 4.15 and 90.4), the request:
   - a. ☐ is not signed.
   - b. ☐ is not signed by all the applicants.
   - c. ☐ is not accompanied by the statement referred to in the check list in Box No. VIII of the request explaining the lack of the signature of an applicant for the designation of the United States of America.
   - d. ☐ is signed by what appears to be an agent/common representative but
     - ☐ the international application is not accompanied by a power of attorney appointing him.
     - ☒ the power of attorney accompanying the international application was not signed by all the applicants.
   - e. ☐ other *(specify)*:

* All applicants must sign, including inventors if they are also applicants (e.g. where the United States of America is designated).

2. As to indications concerning the **applicant**, the request (Rules 4.4 and 4.5):
   - a. ☐ does not properly indicate the applicant's name *(specify)*:
   - b. ☐ does not indicate the applicant's address.
   - c. ☐ does not properly indicate the applicant's address *(specify)*:
   - d. ☐ does not indicate the applicant's nationality.
   - e. ☐ does not indicate the applicant's residence.
   - f. ☐ other *(specify)*:

3. As to the **language** of certain elements of the international application, other than the description and claims (Rules 12.1(c) and 26.3*ter*(a) and (c)):
   - a. ☐ the **request** is not in a language which is both a language accepted by the receiving Office and a language of publication, which is (are): English, French, German
   - b. ☐ the **text matter of the drawings** is not in the language in which the international application is to be published, which is: English, French, German
   - c. ☐ the **abstract** is not in the language in which the international application is to be published, which is: English, French, German

4. The **title** of the invention:
   - a. ☐ is not indicated in Box No. I of the request (Rule 4.1(a)).
   - b. ☐ is not indicated at the top of the first sheet of the description (Rule 5.1(a)).
   - c. ☐ as appearing in Box No. I of the request is not identical with the title heading the description (Rule 5.1(a)).

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
BET 98/1029		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP98/08557	14/12/1998	15/12/1997
International Patent Classification (IPC) or national classification and IPC C12N15/12		
Applicant INSTITUT NATIONAL DE LA SANTE ... et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 10 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 5 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☒ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
07/07/1999	29.03.00
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Julia, P Telephone No. +49 89 2399 8410

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP98/08557

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-30 as originally filed

Claims, No.:

1-25 with telefax of 03/01/2000

Drawings, sheets:

1/8-8/8 as originally filed

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

II. Priority

1. ☐ This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:

☐ copy of the earlier application whose priority has been claimed.

☐ translation of the earlier application whose priority has been claimed.

2. ☐ This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid.

Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

see separate sheet

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-2, 9, 11-17, 19-22, 25
	No:	Claims	3-8, 10, 18, 23-24
Inventive step (IS)	Yes:	Claims	1-2, 9, 13-17, 21-22, 25
	No:	Claims	3-8, 10-12, 18-20, 23-24
Industrial applicability (IA)	Yes:	Claims	1-24
	No:	Claims	25 see citations and explanations)

2. Citations and explanations

see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

1. Additional remarks to item I :

A "Sequence Listing" has been filed with the present application. This "Sequence Listing" comprises SEQ ID No.: 1 to SEQ ID No.: 27 (pages 1-36).

2. Additional remarks to item II :

The priority documents pertaining to the present application were not available at the time of establishing this international preliminary examination report (IPER). Hence, the current assessment is based on the assumption that all claims enjoy priority rights from the filing date of the priority document (15.12.1997). If it later turns out that this is not correct, the documents (a) P. Billuart et al., Nature 1998, Vol. 392, pages 923-926, (b) P. Billuart et al., Médicine/Sciences 1998, Vol. 14, pages 679-681 and (c) P. Billuart et al., Pathologie Biologie 1998, Vol. 46, page 678 cited in the International Search Report (ISR) could become relevant to assess whether the claimed subject matter of the present application satisfies the criteria set forth in Article 33 (1) PCT.

3. Additional remarks to item V :

The present application discloses the nucleotide (and corresponding amino acid sequence) sequence of the oligophrenin 1 gene (figure 3a, SEQ ID No.: 1 5' fragment of the genomic DNA, SEQ ID No.: 2-25 are fragments of the genomic DNA including exons as shown in Tables 1 and 2, SEQ ID No.: 26 is a cDNA fragment corresponding to the common ORF and SEQ ID No.: 27 is the corresponding amino acid sequence, 802 Aa, 91 kDa), which is a non-specific X-linked mental retardation gene (MRX). The oligophrenin 1 protein is a rho-GAP protein (figure 3b comparison with other members of the rho-GAP subfamily) which enhances GTPase activity of small Ras-like GTPases and hence turns them off, i.e. defects in the oligophrenin-1 gene which lead to an inactivation of the protein lead to a constitutive activation of its target GTPases. The protein is thus involved in disorders due to an abnormal neuron migration (misguided axon growth and/or defective cell migration) including apart from MRX, cryptogenic epilepsis and neurodegenerative diseases. The application explicitly claims the nucleic acids disclosed in the application and related ones as well as the corresponding encoded proteins, vectors, host cells, antibodies, uses and methods of diagnosis, pharmaceutical compositions, transgenic non-human animals, a therapeutic method, etc...

The following documents have been cited in the International Search Report (ISR) as being relevant for assessing the novelty and inventiveness of the claimed subject matter:

i) T. Bienvenu et al., Eur. J. Human Genetics 1997, Vol. 5, pages 105-109 (**D1**) is concerned with the mapping of the X-breakpoint involved in a balanced X;12 translocation in a female with mild mental retardation. D1 identifies the genomic critical region involved in said nonspecific mental retardation within the YAC clone 4690 (ICRFy900HO493) of approximately 850 kb in size (containing the PGK1P1, DXS133 and DXS159 loci). Reference is also made to subcloning of the YAC inserts into cosmid vectors and the further interest on fine mapping the breakpoint using pulse field electrophoresis, a cosmid contig covering said breakpoint and other (standard) related techniques (flanking STSs, PCR, etc...). The result of these studies is the identification of the oligophrenin-1 gene (as shown on DATABASE EMBL - Entry HSJ001189, AC = J001189, Chelly et al., 15.04.98), which is actually the contribution of the present application.

The IPEA considers that due to the wording of claim 3 and in particular due to the use of "comprising" (and the reference to an "homologous sequence thereof", see paragraph (i) under item VIII below), which implies that the claimed nucleic acids are not actually limited to specific sequences but they can consist of larger sequences (such as the YAC clone and derived subcloning products disclosed in D1), the subject matter of claims 3, 5 and 6 as well as claims 7 and 8 (as far as they do not exclude such larger sequences and other members of the rho-GAP subfamily) is anticipated by D1 (Articles 33 (2) and (3) PCT).

ii) DATABASE EMBL - EMHTG, Entry HS360E18, AC = Z82203 (**D2**) discloses the nucleotide sequence of the X-chromosome clone 360E18 (approximately 132 kb in size), which according to figure 1a of the present application "comprises" (or "has") several nucleotide sequences claimed in the present application, in particular the ISR refers to nucleotides 16021-17040, 19801-20400, 23401-24420, 43981-45000, 92641-93600 and 108601-109500 (SEQ ID No.: 3, 4, 6, 7, 9 and 10 genomic sequences, each comprising an exon and aligns with SEQ ID No.: 26 over a 130 bp stretch). Thus, such a sequence fulfils the requirements of claims 7-8 (Articles 33 (2) and (3) PCT).

iii) DATABASE EMBL - EMHUM1, Entry HS63M23, AC = Z98754 (**D3**) discloses the nucleotide sequence of the X-chromosome clone 63M23 which according to the ISR is virtually identical to a 723 bp stretch of SEQ ID No.: 25 and thus, it is novelty destroying for the subject matter of claims 7-8 (Articles 33 (2) and (3) PCT).

In view of the actual wording of the claims (in particular the ambiguous meaning of "homologous"), the attention of the Applicant is also drawn to the following considerations: (i) the ESTs (mouse EST483210 and human EST387042 localized on chromosome 11) cited in the description of the present application as having a significant homology to oligophrenin-1 gene, could also anticipate the subject matter of at least claims 7 and 8 and (ii) the same objection would apply for the "homologous" CELT04C95 and CELZK328 (pages 17, 20, 23, etc... and figures 3b and 3c). In this respect and in view of the close homology shown in figures 3b and 3c to well-known products and again due to the broad interpretation of "homologous" (includes any type and/or kind of mutation without any limitation to the actual number of mutations, see page 4 lines 5-7, page 14 lines 29-32 and page 17 lines 21-23), the IPEA considers that the known prior art discloses different polypeptides which are "substantially homologous" (in the broad sense given in the present application) to the claimed oligophrenin 1 and thus, they anticipate the subject matter of claims 4, 10 and 18 (Articles 33 (2) and (3) PCT). Furthermore, the production of antibodies against known polypeptides does not seem to require any inventive contribution from the skilled person and thus, the subject matter of claims 11-12 and 20 does not fulfil the requirements of Article 33 (3) PCT (see also point (v) under "Additional remarks to item VIII" below).

Moreover, as far as the wording of claim 22 is ambiguous and the products or drugs screened by the method of claim 22 are not clearly identified and characterized, the IPEA considers that known "drugs" could fall under the scope of claims 23 and 24, which are thus not seen as novel (Articles 33 (2)and (3) PCT) (see paragraph (ix) under "Additional remarks to item VIII" below).

No prior art cited in the ISR has disclosed the **specific** nucleotide and corresponding **specific** amino acid sequences of oligonephrin 1 and they could not have been derived from this cited prior art in an obvious manner. Thus, the IPEA considers that claims directed to these **specific** sequences as well as claims comprising the particular methods using these **specific** sequences, i.e. in particular the subject matter of claims 1-2 (see however paragraph (i) under item VIII below in respect of "homologous"), 9, 13-17, 21-22 and 25 fulfil the requirements of Articles 33 82) and (3) PCT.

The attention of the Applicant is also drawn to the fact that the subject matter of claim 25 is directed to a method for treatment of the human or animal body and thus, it may be

excluded from examination by Article 34(4)(a)(i) PCT in combination with Rule 67(iv) PCT too. Furthermore, for such a subject matter no unified criteria exist in PCT for the assessment whether it is industrially applicable or not. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject matter of claims to the use of a compound in medical treatment, but will allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

4. Additional remarks to item VII :

i) several bibliographic references cited in the description are not listed and completely given in the reference list on pages 28-30. In particular the references on pages 10 (Antonarakis et al, 1989; Cooper et al., 1991; Bellis et al., 1997) and page 16 (Kohler and Milstein, 1975). On the other hand, several references given in the list of pages 28-30 do not seem to be cited in the description, in particular Gecz et al., 1994; Gedeon et al., 1996; Herbst et al., 1980; M. Kozak, 1986; etc...

ii) page 3 lines 8-9 refers to table 2 as showing exon 25, whereas in said table there are however only exon 1 to exon 24. Page 24 line 26 identifies SEQ ID No.: 26 as an amino acid sequence, whereas SEQ ID No.: 26 is actually a nucleotide sequence.

iii) on page 19 on the description of figure 3a reference is made to a dotted line. However, said dotted line does not seem to be actually present on figure 3a.

5. Additional remarks to item VIII :

The Applicant is reminded that the meaning of a claim must be clear from the wording of the claim alone (PCT-Gazette, Special Issue "PCT-International preliminary Examination Guidelines" 29.10.98, Section IV, Chapter III-4.2). Thus, the following objections are raised under **Article 6 PCT** concerning the clarity of the claims :

i) the wording "homologous" without any further limitation renders the actual scope of the claims completely ambiguous. In fact, as far as the degree of homology is not explicitly disclosed, products being 5, 10%, 15%, etc... homologous already fall under the broad

definition of "homologous". The broad definition on page 4 lines 5-7 concerning nucleic acids (defining general types of modifications but without any limit to the actual number of such possible modifications) as well as the ones on page 5 lines 24-26 (general references to species homologous and allelic variants) and on page 14 lines 29-32 (similar reference to general modifications and to general biological/immunological properties) concerning proteins, do not overcome this objection. In fact only the specific degree of homology makes the scope of the claims clear (see for instance page 4, lines 8-10 and page 15 lines 1-3). This objection applies to the subject matter of claims 1-3, 5, etc...

In this respect too, the wording "substantially" without any further characterization makes the scope of claim 5 ambiguous and open to any possible subjective interpretation. The introduction of any reference to the general "immunological and/or biological" properties of oligonephrin 1 but without clearly defining these activities and/or properties in the wording of the claim would not be overcome this objection. In particular, and due to the cross-reactivity with antibodies raised against other members of the rho-GAP subfamily, the specific immunological properties of oligophrenin 1 are very difficult to define.

ii) general references to "hybridization" without clearly defining the conditions of said hybridization are seen by the IPEA as ambiguous. This objection is relevant for the subject matter of claims 7-8 (refers however to "stringent conditions") and 16-17, 19, etc.... In particular, the wording "specifically" in claims 7-8 is not clear (depends on the conditions, length of the nucleic acid, reference nucleic acid sequences, etc...). In addition and bearing in mind the close similarity of oligonephrin 1 with other members of the rho-GAP subfamily (figure 3b), the IPEA considers that fragments of nucleic acids encoding several members of said family and having the minimum length required in claims 7- 8 (at least 15 bases, i.e. coding at least for 5 residues) would certainly fulfil the requirements of claims 7- 8 (see for instance the fragments with high homology FGPTL, EGLYR. etc...).

iii) the IPEA considers that almost any protein contains portions or domains (as well as small, arbitrary peptides that can be also used as haptens) with a significant homology to similar domains of other completely unrelated proteins (apart from the presence of said domains). These domains do comprise immunoepitopes which can elicit antibodies that cross-react with these unrelated proteins. The production of "specific" antibodies requires the identification of "specific, selective or unique" immunoepitopes, the production of antibodies directed against said immunoepitopes, the demonstration that said antibodies

are able to successfully react against the whole protein (containing such immunoepitopes. It could well be that structural constrains hinder the identification of said immunoepitopes when present in the whole protein) and that they are actually "specific" (and relevant) of said protein. Therefore, the IPEA considers that as far as said "specific" epitopes are not explicitly disclosed in the description or else the production of said "specific" antibodies is not clearly exemplified in the description, such a subject matter is only worded in terms of the result to be achieved and it can not be seen as being **fully** (i.e. formally and technically) supported by the description as required by Article 6 PCT. Furthermore, in view of the significant homology among the claimed oligonephrin 1 protein and other members of the rho-GAP subfamily (figure 3b) as well as to other known proteins (figure 3c), these "specific" epitopes should be clearly and explicitly defined in those claims concerned with "specific" antibodies. Thus, the subject matter directed to a general (monoclonal or polyclonal, fragments thereof, etc...) "antibody specific" for the oligonephrin 1, namely claim 11 (and therefore dependent claims 12, 20, etc...) does not fulfil these requirements.

iv) the method of claim 14 is not characterized by any technical feature. In fact, claim 14 only amounts to recite the result desired to be achieved but there is no technical information which could allow the skilled person to achieve it. In particular, there is no information regarding the actual method and the means used for "detecting" the one or more mutation(s) in the transcript or gene of oligophrenin 1 (in addition, there is no disclosure of any mutation or abnormality actually associated with a neurological disease. This is relevant for the subject matter of claim 13 too). In fact, this is the subject matter of claims 16-17. However, these claims lack clarity as far as an essential technical feature for performing them are the "specific oligonucleotides having a sequence as defined in claims 7-8" which are, however, not clearly characterized (see paragraph (ii) above).

v) the wording of independent claim 19 refers to an "anti-sense sequence as defined in claims 7-8", whereas claims 7-8 are directed to specific nucleic acid sequences and there is no reference to any anti-sense sequence.

vi) the subject matter of claim 21 refers to general "transgenic non-human mammals". Methods for producing transgenic non-human mammalian animals are not general for all mammals and they depend on the specific mammal used. Several steps such as a suitable status (stage) of the egg for optimal introduction of the DNA construct(s), time of insertion

of the egg into the oviduct or uterus, etc.. are critical for the success of the method. Furthermore, several mammalian species do not lend themselves applicable to the present technology used for transgenic mice (or sheep, rabbits, goats and cows), such as duckbill platypus, spiny anteaters (echidna, egg-laying mammals, etc..). The IPEA considers that the description is not enabling for the whole range claimed and that the references cited in the application are only concerned with the production of transgenic mice.

vii) claim 22 is not clear as far as there is no technical step or information concerning the actual method (and means) used for screening the drugs but only a general reference "tested on" without any indication on the result to be expected and the criteria used for actually "selecting" the drugs. In addition, there is neither a technical information concerning the method for rendering the native oligophrenin 1 protein non-functional (method, mutation, type of mutation) nor in which respect (what function is actually rendered inactive or inhibited) the oligophrenin 1 protein is rendered non-functional (see for instance page 12-13, wherein both the method, means, results and criteria are clearly defined) (this applies too for claim 21).The application only discloses one very specific mutation which seems to make the oligophrenin 1 gene inactive, namely the deletion in position 1578 of SEQ ID No.: 26 (example 2).

viii) as far as the method of claim 22 is unclear, any drug can be tested on the systems referred in claim 22 and (positively or negatively) selected on their (likely) activity on the referred signalling pathway. Claims 23 and 24 (and claim 25 partly), independently of the methods used for their screening and/or production, are directed to products "per se" and thus, they can comprise well-known products (which inherently have the ability now disclosed in the present application) falling under their scope. As far as the claimed products are not clearly characterized (structurally, sequences, parameters, etc...), the IPEA considers that this scope is unclear.

CLAIMS

1. Nucleic acid having a sequence selected from the group consisting of sequences SEQ ID n° 1 to SEQ ID n° 25, and a homologous nucleic acid sequence thereof.

2. Nucleic acid having a sequence selected from the group consisting of exon sequences as identified in table 2, and a homologous nucleic acid sequence thereof.

3. Nucleic acid comprising the sequence as shown in SEQ ID n° 26 or a homologous sequence thereof.

4. Nucleic acid comprising a sequence identical to SEQ ID n° 26, except for a one base deletion of the nucleotide 1578 as shown in SEQ ID N° 26.

5. Isolated oligophrenin 1 polypeptide substantially comprising the aminoacid sequence of SEQ ID n° 27, or a homologous amino acid sequence thereof.

6. Vector for cloning and/or expression comprising a nucleic acid sequence of any of claims 1 to 4.

7. Host cell transfected with a vector according to claim 6.

8. Nucleic acid sequence which specifically hybridizes with a nucleic acid sequence according to any of claims 1 to 4.

9. Nucleic acid sequence of claim 8 selected from the group consisting of the sequences identified in table 3 or the complementary sequences thereof.

10. Method for producing a recombining oligophrenin 1 polypeptide, wherein a host cell of claim 7 is transfected with a vector of claim 6 and is cultured in conditions allowing the expression of a polypeptide according to claim 5.

11. Monoclonal or polyclonal antibodies, or fragments thereof, chimeric or immunoconjugate antibobies, which are capable of specifically recognizing a polypeptide according to claim 5.

12. Use of the antibodies of claim 11 for detecting or purifiyng a polypeptide according to claim 5 in a biological sample.

13. Use of a nucleic acid sequence according to any of claims 1, 2, 3, 8 and 9, for detecting an abnormality in the oligophrenin 1 gene or in the transcripts of the oligophrenin 1 gene.

14. Method of *in vitro* diagnosis of a neurological disorder associated with an abnormality in the oligophrenin 1 gene or in the transcripts of the oligophrenin 1 gene, wherein one or more mutation(s) is detected in the oligophrenin 1 gene or in the transcripts of the oligophrenin 1 gene.

15. Method according to claim 14 wherein said mutation is a one base deletion of the nucleotide 1578 as shown in SEQ ID N° 26.

16. Method of *in vitro* diagnosis according to any of claims 14 or 15 comprising the steps of :

- contacting a biological sample containing DNA with specific oligonucleotides permitting the amplification of all or part of the oligophrenin 1 gene, the DNA contained in the sample having being rendered accessible, where appropriate, to hybridization, and under conditions permitting a hybridization of the primers with the DNA contained in the biological sample ;
- amplifying said DNA ;
- detecting the amplification products ;

- comparing the amplified products as obtained to the amplified products obtained with a normal control biological sample, and thereby detecting a possible abnormality in the oligophrenin 1 gene.

17. Method of in vitro diagnosis according to any of claims 14 or 15 comprising the steps of :

- producing cDNA from mRNA contained in a biological sample ;
- contacting said cDNA with specific oligonucleotides permitting the amplification of all or part of the transcript of the oligophrenin 1 gene, under conditions permitting a hybridization of the primers with said cDNA ;
- amplifying said cDNA ;
- detecting the amplification products ;
- comparing the amplified products as obtained to the amplified products obtained with a normal control biological sample, and thereby detecting a possible abnormality in the transcript of the oligophrenin 1 gene.

18. Pharmaceutical composition comprising a purified oligophrenin 1 polypeptide of the invention and/or a homologous polypeptide thereof, or an isolated nucleic acid sequence encoding said polypeptides in association with a pharmaceutically acceptable carrier

19. Pharmaceutical composition comprising an anti-sense sequence capable of specifically hybridizing with a nucleic acid sequence encoding said polypeptides in association with a pharmaceutically acceptable carrier.

20. Pharmaceutical composition comprising an antibody directed against said polypeptides.

21. Transgenic non-human animal expressing an exogenous oligophrenin 1 protein or a mutated native oligophrenin 1 protein.

22. Method for screening drugs likely to act on the signaling pathway to which the oligophrenin 1 protein belongs, wherein said drugs are tested on transgenic non-human animals, or cells in culture, that overexpress oligophrenin 1 protein or preferably express a native oligophrenin 1 protein that has been rendered non-functional.

23. Drug selected by the method of claim 22.

24. Pharmaceutical composition containing a drug of claim 23 in association with a pharmaceutically acceptable carrier.

25. Method of preventing and/or treating neurological disorders resulting from defects in the oligophrenin 1 gene or in the oligophrenin 1 protein or in a homologous gene or protein thereof, which comprises administering to a subject in need of a such treatment an amount of a pharmaceutical composition of claim 18 or 24 effective to prevent and/or alleviate said neurological disorders.

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C12N 15/12 | A2

(11) International Publication Number: **WO 99/31230**

(43) International Publication Date: 24 June 1999 (24.06.99)

(21) International Application Number: PCT/EP98/08557

(22) International Filing Date: 14 December 1998 (14.12.98)

(30) Priority Data:
97403050.4 15 December 1997 (15.12.97) EP

(71) Applicant *(for all designated States except US)*: INSTITUT NATIONAL DE LA SANTE ET DE LA RECHERCHE MEDICALE (INSERM) [FR/FR]; 101, rue de Tolbiac, F–75013 Paris (FR).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: CHELLY, Jamel [FR/FR]; 11, rue Truillot, F–94200 Ivry sur Seine (FR). BILLUART, Pierre [FR/FR]; 5, rue Poliveau, F–75005 Paris (FR). KAHN, Axel [FR/FR]; 10, rue du Docteur Roux, F–75015 Paris (FR). BELDJORD, Cherif [FR/FR]; 11 bis, rue Jacob Courant, F–78300 Poissy (FR).

(74) Agent: LE GUEN, Gérard; Cabinet Lavoix, 2, place d'Estienne d'Orves, F–75441 Parix Cedex 09 (FR).

(81) Designated States: CA, JP, US, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
Without international search report and to be republished upon receipt of that report.

(54) Title: A NEW GENE CALLED OLIGOPHRENIN 1, ITS EXPRESSION PRODUCT, AND THE DIAGNOSTIC AND THERAPEUTIC APPLICATIONS THEREOF

(57) Abstract

The present invention relates to the identification of a new gene, called oligophrenin 1, its expression product, and the diagnostic and therapeutic applications of these nucleotide and peptide sequences.

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PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C12N 15/12, C07K 14/47, A61K 38/17, C12Q 1/68, C12N 15/11, C07K 16/18, A01K 67/027 | A3

(11) International Publication Number: **WO 99/31230**

(43) International Publication Date: 24 June 1999 (24.06.99)

(21) International Application Number: PCT/EP98/08557

(22) International Filing Date: 14 December 1998 (14.12.98)

(30) Priority Data:
97403050.4 15 December 1997 (15.12.97) EP

(71) Applicant *(for all designated States except US)*: INSTITUT NATIONAL DE LA SANTE ET DE LA RECHERCHE MEDICALE (INSERM) [FR/FR]; 101, rue de Tolbiac, F–75013 Paris (FR).

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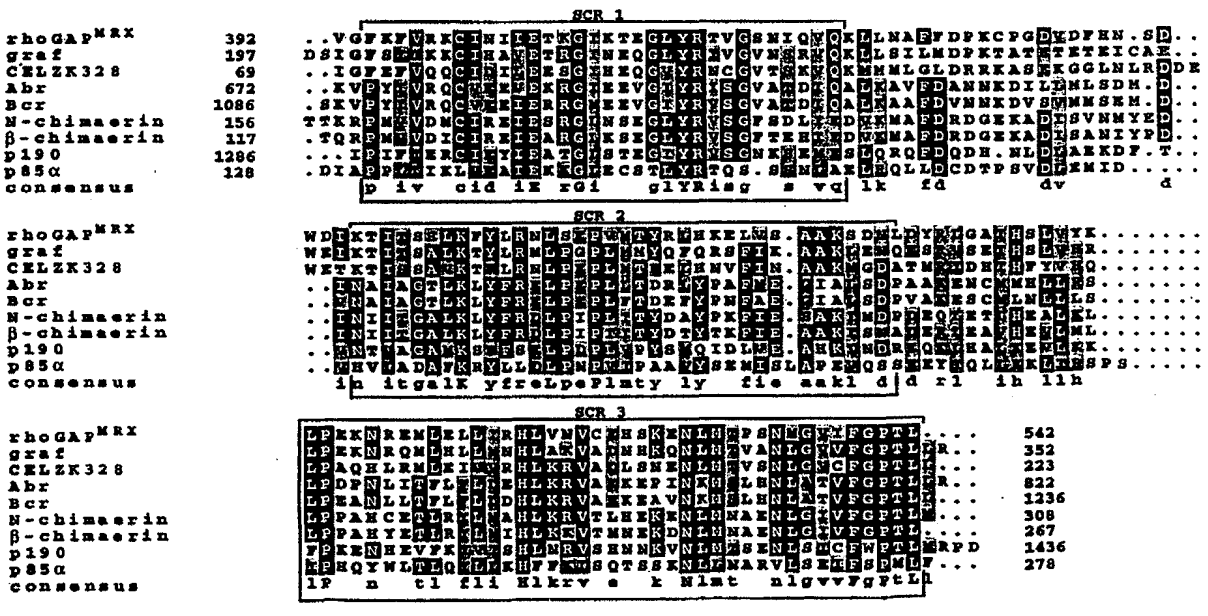
Published

With international search report.

Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(88) Date of publication of the international search report:
12 August 1999 (12.08.99)

(54) Title: OLIGOPHRENIN-1, ITS EXPRESSION PRODUCT, AND THE DIAGNOSTIC AND THERAPEUTIC APPLICATIONS THEREOF



(57) Abstract

The present invention relates to the identification of a new gene, called oligophrenin 1, its expression product, and the diagnostic and therapeutic applications of these nucleotide and peptide sequences.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 98/08557

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C12N15/12 C07K14/47 A61K38/17 C12Q1/68 C12N15/11
C07K16/18 A01K67/027

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C12N C07K A61K C12Q A01K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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[X] Further documents are listed in the continuation of box C.

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Date of the actual completion of the international search	Date of mailing of the international search report
3 June 1999	16/06/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Smalt, R

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INTERNATIONAL SEARCH REPORT

Int. ...al Application No
PCT/EP 98/08557

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE EMBL - EMHTG Entry HS360e18, Acc.No. Z82203, 8 November 1996 WRAY, P.: "Human DNA sequence *** SEQUENCING IN PROGRESS *** from clone 360E18" XP002067478 * nucleotides 16021-17040, 19801-20400, 23401-24420, 43981-45000, 92641-93600, 108601-109500 * ---	1-3,6-8
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 98/ 08557

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
see FURTHER INFORMATION sheet PCT/ISA/210

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Although claim 25 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Claims 23 and 24 could not be searched to completion due to insufficient characterization of the drug in the description.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
BET 98/1029		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/EP 98/ 08557	14/12/1998	15/12/1997
Applicant		
INSTITUT NATIONAL DE LA SANTE ... et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 5 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [X] contained in the international application in written form.

   [X] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [ ] the text is approved as submitted by the applicant.

   [X] the text has been established by this Authority to read as follows:

   OLIGOPHRENIN-1, ITS EXPRESSION PRODUCT, AND THE DIAGNOSTIC AND THERAPEUTIC APPLICATIONS THEREOF

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. 3b

   [ ] as suggested by the applicant.

   [X] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [ ] None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 98/ 08557

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Date of the actual completion of the international search	Date of mailing of the international search report
3 June 1999	16/06/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Smalt, R

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